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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/16, 9/50	A1	(11) International Publication Number: WO 99/16427
		(43) International Publication Date: 8 April 1999 (08.04.99)
<p>(21) International Application Number: PCT/US98/20548</p> <p>(22) International Filing Date: 29 September 1998 (29.09.98)</p> <p>(30) Priority Data: 08/939,939 29 September 1997 (29.09.97) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/939,939 (CON) Filed on 29 September 1997 (29.09.97)</p> <p>(71) Applicant (<i>for all designated States except US</i>): EMISPHERE TECHNOLOGIES, INC. [US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): MILSTEIN, Sam, J. [US/US]; 105 Willow Avenue, Larchmont, NY 10538 (US). LEONE-BAY, Andrea [US/US]; 20 Woodland Way, Ridgefield, CT 06877 (US). SARUBBI, Donald, J. [US/US]; 18 Lawton Lane, Bronxville, NY 10708 (US). LEIPOLD, Harry [US/US]; 63 Town Green Drive, Elmsford, NY 10523 (US).</p> <p>(74) Agents: ROBINSON, Joseph, R. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022-7513 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>		
(54) Title: ACTIVE AGENT TRANSPORT SYSTEMS		
(57) Abstract		
<p>Methods for transporting a biologically active agent across a cellular membrane or a lipid bilayer. A first method includes the steps of: (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to the native state and which is conformationally between the native and denatured states; (b) exposing the biologically active agent to a complexing perturbant to reversibly transform the biologically active agent to the intermediate state and to form a transportable supramolecular complex; and (c) exposing the membrane or bilayer to the supramolecular complex, to transport the biologically active agent across the membrane or bilayer. The perturbant has a molecular weight between about 150 and about 600 daltons, and contains at least one hydrophilic moiety and at least one hydrophobic moiety. The supramolecular complex comprises the perturbant non-covalently bound or complexed with the biologically active agent. In the present invention, the biologically active agent does not form a microsphere after interacting with the perturbant. A method for preparing an orally administrable biologically active agent comprising steps (a) and (b) above is also provided as are oral delivery compositions. Additionally, mimetics and methods for preparing mimetics are contemplated.</p>		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/20548

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) A61K 9/16; 9/50

US CL : 424/ 451, 488, 489, 490, 491

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 451, 488, 489, 490, 491

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS, MEDLINE, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,451,410 A (MILSTEIN et al.) 19 Sept. 1995, see entire document.	1-111
Y	US 5,578,323 A (MILSTEIN et al.) 26 November 1996, see entire document.	1-111
Y	US 5,443,841 A (MILSTEIN et al.) 22 August 1995, see entire document.	1-111

Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"E"	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

30 NOVEMBER 1998

Date of mailing of the international search report

12 JAN 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
LAKSHMI S. CHANNAVAJJALA

Telephone No. (703) 308-0196

IN THE CLAIMS:

1 1. A method for delivering, by the subcutaneous route, a
2 biologically active agent to a subject in need of said biologically active agent,
3 said method comprising:

4 (a) providing a biologically active agent which can exist in a native
5 conformational state, a denatured conformational state, and an intermediate
6 conformational state which is reversible to said native state and is
7 conformationally between said native and denatured states;

8 (b) exposing said biologically active agent to a complexing perturbant
9 to reversibly transform said biologically active agent to said intermediate
10 state and to form a subcutaneously deliverable supramolecular complex,
11 said perturbant having a molecular weight between about
12 150 to about 600 daltons, and having at least one hydrophilic
13 moiety and at least one hydrophobic moiety,

14 said supramolecular complex comprising said perturbant
15 non-covalently complexed with said biologically active agent,

16 said biologically active agent not forming a microsphere
17 with said perturbant, and

18 said perturbant being present in an amount effective for
19 subcutaneous delivery of said biologically active agent; and

20 (c) subcutaneously administering said supramolecular complex to said
21 subject.

1 2. A method as defined in claim 1, further comprising
2 (d) after said administering step, removing said perturbant from
3 said supramolecular complex to transform said biologically active agent to said
4 native state.

1 3. A method as defined in claim 2, wherein step (d) comprises
2 diluting said supramolecular complex.

1 4. A method as defined in claim 1, wherein said intermediate
2 state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles
3 relative to said native state.

1 5. A method as defined in claim 1, wherein said biologically
2 active agent is selected from the group consisting of a peptide, a
3 mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 6. A method as defined in claim 5, wherein said biologically-
2 active agent is selected from the group consisting of human growth hormone,
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,
4 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor,
5 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin,
6 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,
7 vancomycin, desferrioxamine (DFO), or any combination of any of the
8 foregoing.

1 7. A method as defined in claim 1, wherein said perturbant
2 comprises a proteinoid.

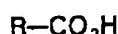
1 8. A method as defined in claim 1, wherein said perturbant is
2 selected from the group consisting of an acylated amino acid and an acylated
3 poly amino acid.

1 9. A method as defined in claim 1, wherein said perturbant is
2 selected from the group consisting of a sulfonated amino acid and a sulfonated
3 poly amino acid.

1 10. A method as defined in claim 1, wherein said perturbant is
2 selected from the group consisting of an acylated aldehyde of an amino acid
3 and an acylated aldehyde of a poly amino acid.

1 11. A method as defined in claim 1, wherein said perturbant is
2 selected from the group consisting of an acylated ketone of an amino acid and
3 an acylated ketone of a poly amino acid.

1 12. A method as defined in claim 1, wherein said perturbant
2 comprises a carboxylic acid having the formula



6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃
7 to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl,
9 phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 13. A method for preparing a subcutaneously deliverable
2 biologically active agent, said method comprising:
3 (a) providing a biologically active agent which can exist in a
4 native conformational state, a denatured conformational state, and an

5 intermediate conformational state which is reversible to said native state and
6 is conformationally between said native and denatured states; and
7 (b) exposing said biologically active agent to a complexing
8 perturbant to reversibly transform said biologically active agent to said
9 intermediate state and to form a subcutaneously deliverable supramolecular
10 complex,

11 said perturbant having a molecular weight ranging from about
12 150 to about 600 daltons, and having at least one hydrophilic moiety
13 and at least one hydrophobic moiety,

14 said supramolecular complex comprising said perturbant
15 non-covalently complexed with said biologically active agent;

16 said biologically active agent not forming a microsphere with said
17 perturbant; and

18 said perturbant being present in an amount effective for
19 subcutaneous delivery of said biologically active agent.

1 14. A method as defined in claim 13, wherein said intermediate
2 state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative
3 to said native state.

1 15. A method as defined in claim 13, wherein said biologically
2 active agent is selected from the group consisting of a peptide, a
3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 16. A method as defined in claim 15, wherein said biologically-
2 active agent is selected from the group consisting of human growth hormone,
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,
4 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor,
5 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin,
6 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,

7 vancomycin, desferrioxamine (DFO), or any combination of any of the
8 foregoing.

1 17. A method as defined in claim 13, wherein said perturbant
2 comprises a proteinoid.

1 18. A method as defined in claim 13, wherein said perturbant
2 is selected from the group consisting of an acylated amino acid and an
3 acylated poly amino acid.

1 19. A method as defined in claim 13, wherein said perturbant
2 is selected from the group consisting of a sulfonated amino acid and a
3 sulfonated poly amino acid.

1 20. A method as defined in claim 13, wherein said perturbant
2 is selected from the group consisting of an acylated aldehyde of an amino acid
3 and an acylated aldehyde of a poly amino acid.

1 21. A method as defined in claim 13, wherein said perturbant
2 is selected from the group consisting of an acylated ketone of an amino acid
3 and an acylated ketone of a poly amino acid

1 22. A method as defined in claim 13, wherein said perturbant
2 comprises a carboxylic acid having the formula

3
4 R-CO₂H
5

6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃
7 to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁
9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;
16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and
18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 23. A subcutaneous delivery composition comprising a
2 supramolecular complex comprising:
3 (a) a biologically active agent in an intermediate
4 conformational state non-covalently complexed with
5 (b) a complexing perturbant having a molecular weight
6 ranging from about 150 to about 600 and having at least one hydrophilic
7 moiety and at least one hydrophobic moiety;
8 wherein said intermediate state is reversible to said native state
9 and is conformationally between a native conformational and a denatured
10 conformational state of said biologically active agent and said composition is
11 not a microsphere; and said perturbant being present in an amount effective
12 for subcutaneous delivery of said biologically active agent.

1 24. A composition as defined in claim 23, wherein said
2 biologically active agent is selected from the group consisting of a peptide, a
3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 25. A composition as defined in claim 24, wherein said
2 biologically-active agent is selected from the group consisting of human
3 growth hormone, bovine growth hormone, growth hormone-releasing
4 hormone, an interferon, interleukin-II, insulin, heparin, calcitonin,

5 erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody,
6 somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,
7 vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any
8 combination of any of the foregoing.

1 26. A composition as defined in claim 23, wherein said
2 perturbant comprises a proteinoid.

1 27. A composition as defined in claim 23, wherein said
2 perturbant is selected from the group consisting of an acylated amino acid and
3 an acylated poly amino acid.

1 28. A composition as defined in claim 46, wherein said
2 perturbant is selected from the group consisting of a sulfonated amino acid
3 and a sulfonated poly amino acid.

1 29. A composition as defined in claim 23, wherein said
2 perturbant is selected from the group consisting of an acylated aldehyde of an
3 amino acid and an acylated aldehyde of a poly amino acid.

1 30. A composition as defined in claim 23, wherein said
2 perturbant is selected from the group consisting of an acylated ketone of an
3 amino acid and an acylated ketone of a poly amino acid.

1 31. A composition as defined in claim 23, wherein said
2 perturbant comprises a carboxylic acid having the formula

4 R-CO₂H

6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃
7 to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁

9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 32. A dosage unit form comprising:

2 (A) a composition as defined in claim 23; and

- 3 (B) (a) an excipient,
4 (b) a diluent,
5 (c) a disintegrant,
6 (d) a lubricant,
7 (e) a plasticizer,
8 (f) a colorant,
9 (g) a dosing vehicle, or
10 (h) any combination thereof.

1 33. A method for preparing an agent which is capable of being
2 deliverable by the subcutaneous route to a subject in need of said agent, said
3 method comprising:

4 (a) providing a biologically active agent which can exist in a
5 native conformational state, a denatured conformational state, and an
6 intermediate conformational state which is reversible to said native state and
7 is conformationally between said native and denatured states;

8 (b) exposing said biologically active agent to a complexing
9 perturbant to reversibly transform said biologically active agent to said

10 intermediate state and to form a subcutaneously deliverable supramolecular
11 complex,
12 said perturbant having a molecular weight between about
13 150 and about 600 daltons, and having at least one hydrophilic moiety and
14 one hydrophilic moiety,
15 said supramolecular complex comprising said perturbant
16 non-covalently complexed with said biologically active agent,
17 said biologically active agent not forming a microsphere
18 with said perturbant, and
19 said perturbant being present in an amount effective for
20 subcutaneous delivery of said biologically active agent; and
21 (c) preparing a mimetic of said supramolecular complex.

1 34. A method as defined in claim 33, wherein said biologically
2 active agent comprises a peptide and said mimetic comprises a peptide
3 mimetic.

1 35. A method for preparing an agent which is capable of being
2 delivered by the subcutaneous route to a subject in need of said agent, said
3 method comprising:
4 (a) providing a biologically active agent which can exist in a
5 native conformational state, a denatured conformational state, and an
6 intermediate which is reversible to said native state and is conformationally
7 between said native and denatured states;
8 (b) exposing said biologically active agent to a perturbant to
9 reversibly transform said biologically active agent to said intermediate state,
10 wherein said perturbant being present in an amount effective for subcutaneous
11 delivery of said biologically active agent; and
12 (c) preparing a mimetic of said intermediate state.

1 36. A method as defined in claim 35, wherein said perturbant
2 comprises a pH changing agent, an ionic strength changing agent, or
3 guanidine hydrochloride.

1 37. A subcutaneous delivery composition comprising a mimetic
2 of the subcutaneous delivery composition prepared by the method of claim 13.

1 38. A method for delivering, by the sublingual route, a
2 biologically active agent to a subject in need of said biologically active agent,
3 said method comprising:

4 (a) providing a biologically active agent which can exist in a
5 native conformational state, a denatured conformational state, and an
6 intermediate conformational state which is reversible to said native state and
7 is conformationally between said native and denatured states;

8 (b) exposing said biologically active agent to a complexing
9 perturbant to reversibly transform said biologically active agent to said
10 intermediate state and to form a subcutaneously deliverable supramolecular
11 complex,

12 said perturbant having a molecular weight between about
13 150 to about 600 daltons, and having at least one hydrophilic
14 moiety and at least one hydrophobic moiety,

15 said supramolecular complex comprising said perturbant
16 non-covalently complexed with said biologically active agent,
17 said biologically active agent not forming a microsphere with said
18 perturbant, and

19 said perturbant being present in an amount effective for
20 sublingual delivery of said biologically active agent; and

21 (c) sublingually administering said supramolecular complex to
22 said subject.

1 39. A method as defined in claim 38, further comprising

2 (d) after said administering step, removing said perturbant from
3 said supramolecular complex to transform said biologically active agent to said
4 native state.

1 40. A method as defined in claim 39, wherein step (d)
2 comprises diluting said supramolecular complex.

1 41. A method as defined in claim 38, wherein said intermediate
2 state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles
3 relative to said native state.

1 42. A method as defined in claim 38, wherein said biologically
2 active agent is selected from the group consisting of a peptide, a
3 mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 43. A method as defined in claim 42, wherein said biologically-
2 active agent is selected from the group consisting of human growth hormone,
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,
4 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor,
5 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin,
6 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,
7 vancomycin, desferrioxamine (DFO), or any combination of any of the
8 foregoing.

1 44. A method as defined in claim 38, wherein said perturbant
2 comprises a proteinoid.

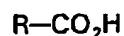
1 45. A method as defined in claim 38, wherein said perturbant
2 is selected from the group consisting of an acylated amino acid and an
3 acylated poly amino acid.

1 46. A method as defined in claim 38, wherein said perturbant
2 is selected from the group consisting of a sulfonated amino acid and a
3 sulfonated poly amino acid.

1 47. A method as defined in claim 38, wherein said perturbant
2 is selected from the group consisting of an acylated aldehyde of an amino acid
3 and an acylated aldehyde of a poly amino acid.

1 48. A method as defined in claim 38, wherein said perturbant
2 is selected from the group consisting of an acylated ketone of an amino acid
3 and an acylated ketone of a poly amino acid.

1 49. A method as defined in claim 38, wherein said perturbant
2 comprises a carboxylic acid having the formula



6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃
7 to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl,
9 phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 50. A method for preparing a sublingually deliverable
2 biologically active agent, said method comprising:

3 (a) providing a biologically active agent which can exist in a native
4 conformational state, a denatured conformational state, and an intermediate
5 conformational state which is reversible to said native state and is
6 conformationally between said native and denatured states; and

7 (b) exposing said biologically active agent to a complexing perturbant
8 to reversibility transform said biologically active agent to said intermediate
9 state and to form a sublingually deliverable supramolecular complex,

10 said perturbant having a molecular weight ranging from about
11 150 to about 600 daltons, and having at least one hydrophilic moiety
12 and at least one hydrophobic moiety,

13 said supramolecular complex comprising said perturbant
14 non-covalently complexed with said biologically active agent;

15 said biologically active agent not forming a microsphere with said
16 perturbant; and

17 said perturbant being present in an amount effective for
18 sublingual delivery of said biologically active agent.

1 51. A method as defined in claim 50, wherein said intermediate
2 state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative
3 to said native state.

1 52. A method as defined in claim 50, wherein said biologically
2 active agent is selected from the group consisting of a peptide, a
3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 53. A method as defined in claim 52, wherein said biologically-
2 active agent is selected from the group consisting of human growth hormone,
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,
4 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor,

5 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin,
6 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,
7 vancomycin, desferrioxamine (DFO), or any combination of any of the
8 foregoing.

1 54. A method as defined in claim 50, wherein said perturbant
2 comprises a proteinoid.

1 55. A method as defined in claim 50, wherein said perturbant
2 is selected from the group consisting of an acylated amino acid and an
3 acylated poly amino acid.

1 56. A method as defined in claim 50, wherein said perturbant
2 is selected from the group consisting of a sulfonated amino acid and a
3 sulfonated poly amino acid.

1 57. A method as defined in claim 50, wherein said perturbant
2 is selected from the group consisting of an acylated aldehyde of an amino acid
3 and an acylated aldehyde of a poly amino acid.

1 58. A method as defined in claim 50, wherein said perturbant
2 is selected from the group consisting of an acylated ketone of an amino acid
3 and an acylated ketone of a poly amino acid.

1 59. A method as defined in claim 50, wherein said perturbant
2 comprises a carboxylic acid having the formula



6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to
7 C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁

9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 60. A sublingual delivery composition comprising a
2 supramolecular complex comprising:

3 (a) a biologically active agent in an intermediate conformational state
4 non-covalently complexed with

5 (b) a complexing perturbant having a molecular weight ranging from
6 about 150 to about 600 and having at least one hydrophilic moiety and at
7 least one hydrophobic moiety;

8 wherein said intermediate state is reversible to said native state
9 and is conformationally between a native conformational and a denatured
10 conformational state of said biologically active agent and said composition is
11 not a microsphere; and said perturbant being present in an amount effective
12 for sublingual delivery of said biologically active agent.

1 61. A composition as defined in claim 60, wherein said
2 biologically active agent is selected from the group consisting of a peptide, a
3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 62. A composition as defined in claim 61, wherein said
2 biologically-active agent is selected from the group consisting of human

3 growth hormone, bovine growth hormone, growth hormone-releasing
4 hormone, an interferon, interleukin-II, insulin, heparin, calcitonin,
5 erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody,
6 somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,
7 vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any
8 combination of any of the foregoing.

1 63. A composition as defined in claim 60, wherein said
2 perturbant comprises a proteinoid.

1 64. A composition as defined in claim 60, wherein said
2 perturbant is selected from the group consisting of an acylated amino acid and
3 an acylated poly amino acid.

1 65. A composition as defined in claim 60, wherein said
2 perturbant is selected from the group consisting of a sulfonated amino acid
3 and a sulfonated poly amino acid.

1 66. A composition as defined in claim 60, wherein said
2 perturbant is selected from the group consisting of an acylated aldehyde of an
3 amino acid and an acylated aldehyde of a poly amino acid.

1 67. A composition as defined in claim 60, wherein said
2 perturbant is selected from the group consisting of an acylated ketone of an
3 amino acid and an acylated ketone of a poly amino acid.

1 68. A composition as defined in claim 60, wherein said
2 perturbant comprises a carboxylic acid having the formula

3

4 R—CO₂H

5

6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to
7 C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C,
9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C,
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 69. A dosage unit form comprising:

2 (A) a composition as defined in claim 60; and

3 (B) (a) an excipient,

4 (b) a diluent,

5 (c) a disintegrant,

6 (d) a lubricant,

7 (e) a plasticizer,

8 (f) a colorant,

9 (g) a dosing vehicle, or

10 (h) any combination thereof.

1 70. A method for preparing an agent which is capable of being
2 administered by the sublingual route to a subject in need of said agent, said
3 method comprising:

4 (a) providing a biologically active agent which can exist in a native
5 conformational state, a denatured conformational state, and an intermediate

6 conformational state which is reversible to said native state and is
7 conformationally between said native and denatured states;
8 (b) exposing said biologically active agent to a complexing perturbant
9 to reversibly transform said biologically active agent to said intermediate state
10 and to form a sublingually administrable supramolecular complex,
11 said perturbant having a molecular weight between about 150 and
12 about 600 daltons, and having at least one hydrophilic moiety and one
13 hydrophilic moiety,
14 said supramolecular complex comprising said perturbant non-covalently
15 complexed with said biologically active agent,
16 said biologically active agent not forming a microsphere with said
17 perturbant; and
18 said perturbant being present in an amount effective for sublingual
19 delivery of said biologically active agent; and
20 (c) preparing a mimetic of said supramolecular complex.

1 71. A method as defined in claim 70, wherein said biologically
2 active agent comprises a peptide and said mimetic comprises a peptide
3 mimetic.

1 72. A method for preparing an agent which is capable of being
2 administered by the sublingual route to a subject in need of said agent, said
3 method comprising:
4 (a) providing a biologically active agent which can exist in a native
5 conformational state, a denatured conformational state, and an intermediate
6 which is reversible to said native state and is conformationally between said
7 native and denatured states;
8 (b) exposing said biologically active agent to a perturbant to
9 reversibly transform said biologically active agent to said intermediate state,
10 wherein said perturbant is in an amount effective for sublingual delivery of said
11 biologically active agent; and
12 (c) preparing a mimetic of said intermediate state.

1 73. A method as defined in claim 72, wherein said perturbant
2 comprises a pH changing agent, an ionic strength changing agent, or
3 guanidine hydrochloride.

1 74. An oral delivery composition comprising a mimetic of the
2 oral delivery composition prepared by the method of claim 50.

1 75. A method for delivering, by the intranasal route, a
2 biologically active agent to a subject in need of said biologically active agent,
3 said method comprising:

4 (a) providing a biologically active agent which can exist in a native
5 conformational state, a denatured conformational state, and an intermediate
6 conformational state which is reversible to said native state and is
7 conformationally between said native and denatured states;

8 (b) exposing said biologically active agent to a complexing perturbant
9 to reversibly transform said biologically active agent to said intermediate
10 state and to form an intranasally administrable supramolecular complex,

11 said perturbant having a molecular weight between about
12 150 to about 600 daltons, and having at least one hydrophilic
13 moiety and at least one hydrophobic moiety,

14 said supramolecular complex comprising said perturbant
15 non-covalently complexed with said biologically active agent,

16 said biologically active agent not forming a microsphere
17 with said perturbant, and

18 said perturbant being present in an amount effective for
19 intranasal delivery of said biologically active agent; and

20 (c) intranasally administering said supramolecular complex to said
21 subject.

1 76. A method as defined in claim 75, further comprising

2 (d) after said administering step, removing said perturbant from
3 said supramolecular complex to transform said biologically active agent to said
4 native state.

1 77. A method as defined in claim 76, wherein step (d)
2 comprises diluting said supramolecular complex.

1 78. A method as defined in claim 75, wherein said intermediate
2 state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles
3 relative to said native state.

1 79. A method as defined in claim 75, wherein said biologically
2 active agent is selected from the group consisting of a peptide, a
3 mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 80. A method as defined in claim 79, wherein said biologically-
2 active agent is selected from the group consisting of human growth hormone,
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,
4 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor,
5 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin,
6 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,
7 vancomycin, desferrioxamine (DFO), or any combination of any of the
8 foregoing.

1 81. A method as defined in claim 75, wherein said perturbant
2 comprises a proteinoid.

1 82. A method as defined in claim 75, wherein said perturbant
2 is selected from the group consisting of an acylated amino acid and an
3 acylated poly amino acid.

1 83. A method as defined in claim 75, wherein said perturbant
2 is selected from the group consisting of a sulfonated amino acid and a
3 sulfonated poly amino acid.

1 84. A method as defined in claim 75, wherein said perturbant
2 is selected from the group consisting of an acylated aldehyde of an amino acid
3 and an acylated aldehyde of a poly amino.

1 85. A method as defined in claim 75, wherein said perturbant
2 is selected from the group consisting of an acylated ketone of an amino acid
3 and an acylated ketone of a poly amino acid.

1 86. A method as defined in claim 75, wherein said perturbant
2 comprises a carboxylic acid having the formula



5
6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to
7 C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁
9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 87. A method for preparing an intranasally deliverable
2 biologically active agent, said method comprising:

3 (a) providing a biologically active agent which can exist in a native
4 conformational state, a denatured conformational state, and an intermediate
5 conformational state which is reversible to said native state and is
6 conformationally between said native and denatured states; and

7 (b) exposing said biologically active agent to a complexing perturbant
8 to reversibility transform said biologically active agent to said intermediate
9 state and to form an intranasally administrable supramolecular complex,

10 said perturbant having a molecular weight ranging from about
11 150 to about 600 daltons, and having at least one hydrophilic moiety
12 and at least one hydrophobic moiety,

13 said supramolecular complex comprising said perturbant
14 non-covalently complexed with said biologically active agent; and

15 said biologically active agent not forming a microsphere with said
16 perturbant;

17 said perturbant being present in an amount effective for intranasal
18 delivery of said biologically active agent.

1 88. A method as defined in claim 87, wherein said intermediate
2 state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative
3 to said native state.

1 89. A method as defined in claim 87, wherein said biologically
2 active agent is selected from the group consisting of a peptide, a
3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 90. A method as defined in claim 89, wherein said biologically-
2 active agent is selected from the group consisting of human growth hormone,
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,
4 interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor,

5 an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin,
6 gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium,
7 vancomycin, desferrioxamine (DFO), or any combination of any of the
8 foregoing.

1 91. A method as defined in claim 87, wherein said perturbant
2 comprises a proteinoid.

1 92. A method as defined in claim 87, wherein said perturbant
2 is selected from the group consisting of an acylated amino acid and an
3 acylated poly amino acid.

1 93. A method as defined in claim 87, wherein said perturbant
2 is selected from the group consisting of a sulfonated amino acid and a
3 sulfonated poly amino acid.

1 94. A method as defined in claim 87, wherein said perturbant
2 is selected from the group consisting of an acylated aldehyde of an amino acid
3 and an acylated aldehyde of a poly amino acid.

1 95. A method as defined in claim 87, wherein said perturbant
2 is selected from the group consisting of an acylated ketone of an amino acid
3 and an acylated ketone of a poly amino acid.

1 96. A method as defined in claim 87, wherein said perturbant
2 comprises a carboxylic acid having the formula

3
4 R-CO₂H

6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to
7 C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁

9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 97. An intranasal delivery composition comprising a
2 supramolecular complex comprising:

3 (a) a biologically active agent in an intermediate conformational state
4 non-covalently complexed with

5 (b) a complexing perturbant having a molecular weight ranging from
6 about 150 to about 600 and having at least one hydrophilic moiety and at
7 least one hydrophobic moiety;

8 wherein said intermediate state is reversible to said native state
9 and is conformationally between a native conformational and a denatured
10 conformational state of said biologically active agent and said composition is
11 not a microsphere; and said perturbant being present in an amount effective
12 for intranasal delivery of said biologically active agent.

1 98. A composition as defined in claim 97, wherein said
2 biologically active agent is selected from the group consisting of a peptide, a
3 micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination
4 of the foregoing.

1 99. A composition as defined in claim 98, wherein said
2 biologically-active agent is selected from the group consisting of human

3 growth hormone, bovine growth hormone, growth hormone-releasing
4 hormone, an interferon, interleukin-II, insulin, heparin, calcitonin,
5 erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody,
6 somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,
7 vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any
8 combination of any of the foregoing.

1 100. A composition as defined in claim 97, wherein said
2 perturbant comprises a proteinoid.

1 101. A composition as defined in claim 97, wherein said
2 perturbant is selected from the group consisting of an acylated amino acid and
3 an acylated poly amino acid.

1 102. A composition as defined in claim 97, wherein said
2 perturbant is selected from the group consisting of a sulfonated amino acid
3 and a sulfonated poly amino acid.

1 103. A composition as defined in claim 97, wherein said
2 perturbant is selected from the group consisting of an acylated aldehyde of an
3 amino acid and an acylated aldehyde of a poly amino acid.

1 104. A composition as defined in claim 97, wherein said
2 perturbant is selected from the group consisting of an acylated ketone of an
3 amino acid and an acylated ketone of a poly amino acid.

1 105. A composition as defined in claim 97, wherein said
2 perturbant comprises a carboxylic acid having the formula

3



5

6 wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to
7 C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀
8 alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁
9 to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and
10 naphthyl(C₂ to C₁₀ alkenyl);

11 R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁
12 to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl,
13 heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more
14 atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁
15 to C₁₀)alkyl, or any combination thereof;

16 R being optionally interrupted by oxygen, nitrogen, sulfur, or any
17 combination thereof; and

18 R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
19 a salt thereof.

1 **106. A dosage unit form comprising:**

2 (A) a composition as defined in claim 97; and

- 3 (B) (a) an excipient,
4 (b) a diluent,
5 (c) a disintegrant,
6 (d) a lubricant,
7 (e) a plasticizer,
8 (f) a colorant,
9 (g) a dosing vehicle, or
10 (h) any combination thereof.

1 **107. A method for preparing an agent which is capable of being**
2 administered by the intranasal route to a subject in need of said agent, said
3 method comprising:

4 (a) providing a biologically active agent which can exist in a native
5 conformational state, a denatured conformational state, and an intermediate

6 conformational state which is reversible to said native state and is
7 conformationally between said native and denatured states;

8 (b) exposing said biologically active agent to a complexing perturbant
9 to reversibly transform said biologically active agent to said intermediate state
10 and to form an intranasally administrable supramolecular complex,

11 said perturbant having a molecular weight between about 150 and
12 about 600 daltons, and having at least one hydrophilic moiety and one
13 hydrophilic moiety,

14 said supramolecular complex comprising said perturbant non-covalently
15 complexed with said biologically active agent,

16 said biologically active agent not forming a microsphere with said
17 perturbant, and

18 said perturbant being present in an amount effective for intranasal
19 delivery of said biologically active agent; and

20 (c) preparing a mimetic of said supramolecular complex.

1 108. A method as defined in claim 107, wherein said biologically
2 active agent comprises a peptide and said mimetic comprises a peptide
3 mimetic.

1 109. A method for preparing an agent which is capable of being
2 administered by the intranasal route to a subject in need of said agent, said
3 method comprising:

4 (a) providing a biologically active agent which can exist in a native
5 conformational state, a denatured conformational state, and an intermediate
6 which is reversible to said native state and is conformationally between said
7 native and denatured states;

8 (b) exposing said biologically active agent to a perturbant to
9 reversibly transform said biologically active agent to said intermediate state,
10 wherein said perturbant is in an amount effective for intranasal delivery of said
11 biologically active agent; and

12 (c) preparing a mimetic of said intermediate state.

1 110. A method as defined in claim 109, wherein said perturbant
2 comprises a pH changing agent, an ionic strength changing agent, or
3 guanidine hydrochloride.

1 111. An oral delivery composition comprising a mimetic of the
2 oral delivery composition prepared by the method of claim 87.